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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification 6 :</b> A61K 9/51, 9/16, 38/13, 31/575, 31/215, 47/10, 47/24		<b>A3</b>	<b>(11) International Publication Number:</b> <b>WO 99/49846</b> <b>(43) International Publication Date:</b> 7 October 1999 (07.10.99)
<b>(21) International Application Number:</b> PCT/US99/06746 <b>(22) International Filing Date:</b> 29 March 1999 (29.03.99)  <b>(30) Priority Data:</b> 60/079,809 30 March 1998 (30.03.98) US		<b>(81) Designated States:</b> AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIGO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
<b>(71) Applicant:</b> RTP PHARMA INC. [US/US]; 4364 South Alston Avenue, Durham, NC 27713-2280 (US). <b>(72) Inventors:</b> KHAN, Sheema; Unit H, 22 Bayshore Drive, Napean, Ontario K2B 6M8 (CA). PACE, Gary, W.; 4364 South Alston Avenue, Durham, NC 27713-2280 (US). <b>(74) Agent:</b> CRAWFORD, Arthur, R.; Nixon & Vanderhye P.C., 8th floor, 1100 North Glebe Road, Arlington, VA 22201-4714 (US).		<b>(88) Date of publication of the international search report:</b> 18 November 1999 (18.11.99)	
<b>(54) Title:</b> COMPOSITIONS CONTAINING MICROPARTICLES OF WATER-INSOLUBLE SUBSTANCES AND METHOD FOR THEIR PREPARATION  <b>(57) Abstract</b> <p>Compositions and procedures that yield sub-micron and micron-size stable particles of water-insoluble or poorly soluble drugs or other industrially useful insoluble compounds are prepared using combinations of natural or synthetic phospholipids, a charged surface modifier such as a highly purified charged phospholipid and a block copolymer coated or adhered onto the surfaces of the water insoluble-compound particles. The combination of charged surface modifier and block copolymer allows the formation and stabilization of the sub-micron and micron size compound particles – stabilized by the charged phospholipid to provide electrostatic stabilization and the block copolymer to provide steric stabilization – and therefore prevents these particles from particle growth, aggregation or flocculation.</p>			

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# INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/06746

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/51 A61K9/16 A61K38/13 A61K31/575 A61K31/215
A61K47/10 A61K47/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 98 07414 A (RES TRIANGLE PHARMACEUTICALS L) 26 February 1998 (1998-02-26) abstract page 1, line 4 - line 14 page 2, line 26 - page 4, line 17 page 5, line 12 - page 6, line 14 page 7, line 4 - line 9 examples 1,2 claims 1-17</p> <p>---</p> <p style="text-align: center;">-/-</p>	1-13

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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- \*E\* earlier document but published on or after the international filing date
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- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*& document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 July 1999	29 September 1999

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# INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/06746

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 97 14407 A (RES TRIANGLE PHARMACEUTICALS ;UNIV TEXAS (US); HENRIKSEN INGE B (U) 24 April 1997 (1997-04-24)</p> <p>abstract</p> <p>page 1, line 20 - page 2, line 2</p> <p>page 3, line 10 - line 27</p> <p>page 4, line 17 - page 6, line 18</p> <p>page 10, line 3 - line 14</p> <p>example 1</p> <p>claims 1-17</p> <p>---</p>	1-13
X	<p>GUZMAN M: "FORMATION AND CHARACTERIZATION OF CYCLOSPORINE-LOADED NANOPARTICLES" JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 82, no. 5, 1 May 1993 (1993-05-01), pages 498-502, XP000368107 ISSN: 0022-3549</p> <p>abstract</p> <p>---</p>	1-13
X	<p>EP 0 499 299 A (STERLING WINTHROP INC) 19 August 1992 (1992-08-19)</p> <p>abstract</p> <p>page 3, line 19 - line 53</p> <p>page 4, line 16 - line 47</p> <p>claims 1-20</p> <p>---</p>	1-13
A	<p>WO 96 24332 A (NANOSYSTEMS LLC) 15 August 1996 (1996-08-15)</p> <p>abstract</p> <p>page 1, line 5 - line 14</p> <p>examples 1-4</p> <p>claims 1-6</p> <p>---</p>	1-13
E	<p>WO 99 29300 A (MISHRA AWADHESH K ;PARIKH INDU (CA); MOUSSA ISKANDAR (CA); RTP PHA) 17 June 1999 (1999-06-17)</p> <p>abstract</p> <p>page 5, line 19 - page 6, line 3</p> <p>examples 1-14</p> <p>claims 1-18</p> <p>-----</p>	1-13

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 99/06746

### Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.: 1,2,12,13 because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
  
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

#### Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

Continuation of Box I.2

Claims Nos.: 1,2,12,13

Present claims 1, 2, 12 and 13 relate to a product/method defined by reference to a desirable characteristic or property, namely that

"the charged surface modifier provides electrostatic stabilisation and the block copolymer provides steric stabilisation against Ostwald ripening and particle aggregation and provides for small particle formation"

The claims cover all products/methods having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such products/methods. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product/method by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the products/methods, namely

the block co-polymers as defined in claim 3, and

the charged surface modifiers as defined in claim 6.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International Application No

PCT/US 99/06746

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